

REMARKS/Arguments**35 U.S.C. § 102**

The Office has maintained this rejection on the same grounds as in the previous action. The Office argues that “[t]here is no indication in the claims that the required cyclodextrin derivative...must be essentially ‘cyclodextrin which has been chemically modified.’”

With all due respect, Applicants point to the specification, p. 8, which states “the term ‘cyclodextrin derivative’...refers to a compound or a mixture of compounds wherein one or more of the free hydroxyl groups of α -, β -, or γ -cyclodextrin is replaced by any other group” (lines 20-23). Applicants remind the Office that a claim term has the meaning given to it in the specification: “[u]sually, [the specification] is dispositive; it is the single best guide to the meaning of a disputed term.” *Phillips v. AWH Corp.* 415 F.3d 1303, 1315 (Fed. Cir.,2005). Thus, in the claims of the present application, the term “cyclodextrin derivative” must be “a compound or a mixture of compounds wherein one or more of the free hydroxyl groups of α -, β -, or γ -cyclodextrin is replaced by any other group.”

Lipari does not teach a cyclodextrin derivative. Rather, it states “[b]eta-cyclodextrin is a cyclic polymer containing seven D-glucose units and is produced by reaction of *Bacillus macerans* amylase on starch. It has a molecular weight of 1135 ...One end of the cavity is edged with -CH₂OH groups (one per glucose unit) and the other rim is edged with secondary -CHOH groups.” (Column 2, lines 10-19.) Thus, none of the free hydroxyl groups are replaced by another group in Lipari’s description, and the molecular weight of unmodified cyclodextrin is 1135. Therefore, Lipari clearly refers only to the unmodified β -cyclodextrin, and Lipari does not anticipate the claims.

35 U.S.C. § 103

The Office is maintaining its obviousness rejection on the same grounds as the previous action. With regard to the *prima facie* case of obviousness, Applicants respectfully disagree on the same basis as that argued in the previous action and add that Applicants disagree that “Loftsson teaches how to overcome” the bioavailability problem as asserted by the Office. Applicants do not consider “can, at least partly, be overcome” and “can sometimes be overcome” to be sufficiently strong assertions by Loftsson to overcome the known problems of formulating cyclodextrins and cyclodextrin derivatives.

Even if the Office did make a *prima facie* case, Applicants point out that it appears that the Office did not consider the unexpected results presented in the specification. Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. MPEP 2144.08 (b)(6) Unexpected results are shown in relation to the closest prior art, but the closest prior art need not be something relied upon by Examiner. *In re Holladay*, 584 F.2d, 384, 386 (CCPA, 1978).

The closest prior art

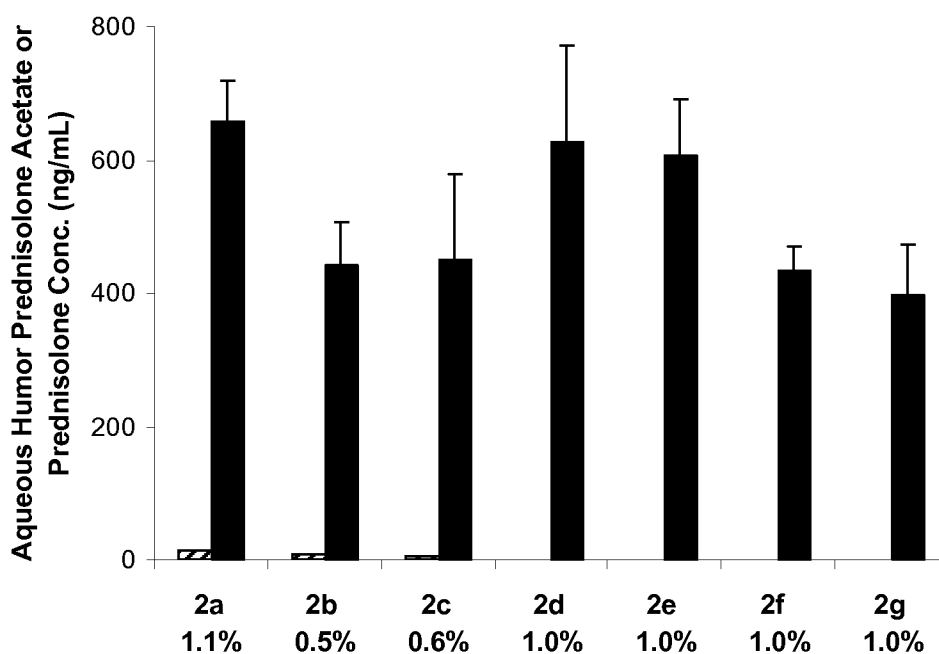
The closest prior art is that which would most likely be used for the same purpose as the claimed composition. The intended use of the claimed composition is the delivery of prednisolone acetate to the ocular tissue for the treatment of inflammation. The commercially available 1% prednisolone acetate suspension is the composition most likely to be used by a person of ordinary skill in the art for that purpose. Therefore, it is the closest prior art.

The unexpected results

In discussing ophthalmic compositions of steroids, Loftsonna states “[f]or diseases of the posterior segments of the eye, systemic administration is required.” (p. 74, right column, section 9.2, end of first paragraph.) Loftsonna

believes that any bioavailability enhancement attributed to cyclodextrin is due to the ability of cyclodextrin to get more drug into solution, and not to any enhanced membrane permeability attributed to cyclodextrin or complexes between cyclodextrins and drugs. Consider the following statements in the Loftsson Paper: “[i]n general, the natural CDs and their hydrophilic derivatives are only able to penetrate lipophilic biological membranes, such as the eye cornea, *with considerable difficulty*.” (p. 62, under “3. Toxicological considerations,” second sentence.) “It is not likely that large hydrophilic CD molecules permeate into those lipophilic membranes.” (p. 63, left column, about $\frac{3}{4}$ from top.) “CD molecules will only permeate biological membranes with considerable difficulty.” (p. 64, left column, third line from bottom.)

Figure 2

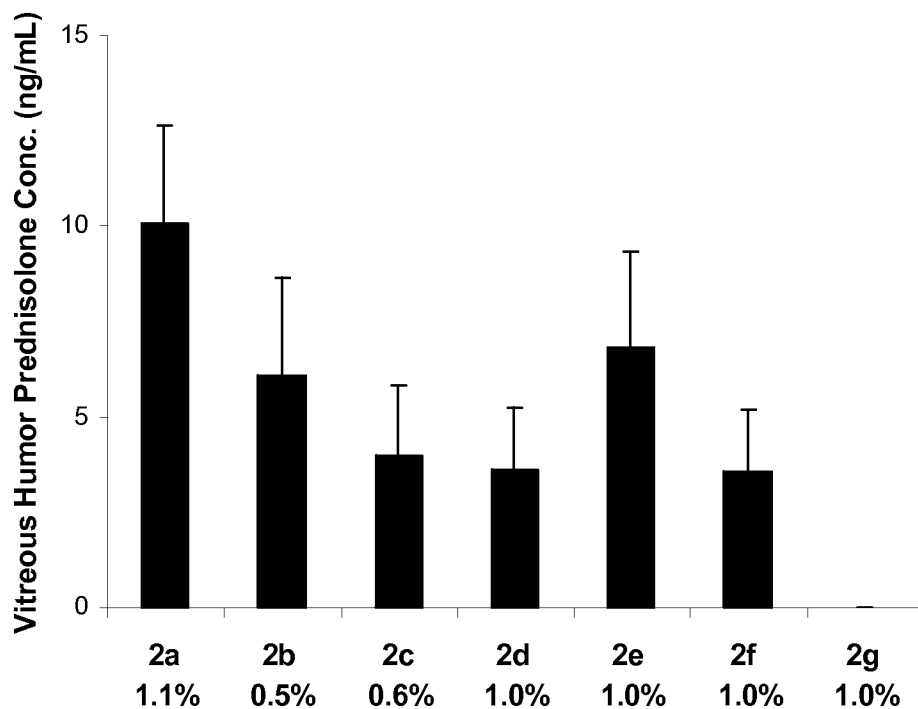


Reproduced above is Figure 2 from the present patent application. This Figure depicts the prednisolone concentration in the aqueous humor arising from the topical administration of several compositions containing prednisolone acetate and a cyclodextrin derivative (2a-2f). Composition 2g is the commercial prednisolone acetate suspension-the closest prior art. Within experimental error,

compositions 2b, 2c, and 2f provide the same prednisolone concentration in the aqueous humor as the closest prior art composition 2g. Since “CD molecules will only permeate biological membranes with considerable difficulty,” a person of ordinary skill in the art would not expect that any CD will be present in the aqueous humor, since it is protected by several biological membranes. If this is the case, one of ordinary skill in the art would not expect to see any difference, within experimental error, in the vitreous humor concentration of prednisolone for 2b, 2c and 2f as compared to 2g.

But, as is easily seen in Figure 3 from the application, reproduced below, there is a significant difference. In fact, the control compound provides no detectable prednisolone to the vitreous humor. This is truly unexpected.

Figure 3



Therefore, the claims are not obvious because of these unexpected results, regardless of whether or not a prima facie case of obviousness was made.

In view of the arguments and the amendments made herein, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Please use Deposit Account 01-0885 for any fee or refund related to this response.

Respectfully submitted,

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